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13. ABSTRACT *(Maximum 200 Words)*

The purpose of this proposal is to research the association of insulin resistance and its joint effect with insulin like growth factors (IGFs) on breast cancer risk. Many epidemiological studies have investigated the association of body weight, fat distribution, and physical activity with the risk of breast cancer. Some studies have compared levels of C-peptide and IGFs between breast cancer cases and controls. None of these studies, however, has evaluated the potential joint effect of C-peptide, IGFs and energy balance on the etiology of breast cancer.

The specific aims of this proposal are 1) To determine blood levels of C-peptide and IGF1, IGF2, and IGFPB3 in a subset of subjects (400 case-control pairs) from the Shanghai Breast Cancer Study (SBCS) (R01CA64277) using pre-treatment blood samples and to evaluate the association of blood C-peptide level and its joint effect with IGFs with the risk of breast cancer. 2) To analyze data collected from the SBCS to evaluate the association of energy balance with breast cancer risk. There is evidence to suggest that the combined effects of positive energy balance result in increased breast cancer risk and that C-peptide level is potentially related to the risk of breast cancer enhanced by IGF bioavailability.

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Table of Contents

Insulin Resistance, IGFs and Energy Balance on the Risk of Breast Cancer

Introduction

Subject: A number of studies have investigated the role of the insulin like growth factors (IGFs), IGF1 and IGF2 and extracellular IGF- binding protein-3 on breast cancer risk. IGF1, IGF2 have been shown to be potent mitogens for a number of breast cancer epithelial lines *in vitro* and as detectable in the majority of human breast tumors. IGF1 and IGF2 together may have a growth promoting role in human breast cancer, but the relationship with these IGFs and IGFBP3 is still inconclusive. IGF1 is bound with high affinity to IGFBP3 prolonging the plasma half-life of IGF1 and having a limiting effect on the availability of IGF1 for biological activity. Several studies have hypothesized that altered levels of IGF1 and IGFBP3 might increase susceptibility to breast carcinogenesis and selection of more aggressive breast tumors. The bioavailability of IGF1 to the tissues modulated by IGFBP3 and higher circulating levels of IGF1 and lower levels of IGFBP3 have been reported in breast cancer patients. It is not clear why IGFBP3 levels in the serum are decreased in cancer patients, but proteolysis of IGFBP3 is regulated by insulin levels and increased in adults with non-insulin-dependent diabetes. This might account for the decreased IGFBP3 in patients with breast cancer associated with hyperinsulinemia. **Purpose:** To analyze data collected from the Shanghai Breast Cancer Study to evaluate the association of energy balance with breast cancer risk. There is evidence to suggest that the combined effects of positive energy balance result in increased breast cancer risk and that C-peptide level is potentially related to the risk of breast cancer enhanced by IGF bioavailability. The link between insulin resistance, IGF1 and risk of breast cancer may be due to the effect of insulin in amplifying the IGF1 action at the breast tissue level. The biological mechanism proposed to explain this association is increased levels of free IGF1 which may act synergistically with estrogen to promote mammary carcinogensis. Thus, it is conceivable that insulin may interact with IGFs in the pathologenesis of breast cancer risk. **Scope:** Limited population-based research has been performed to evaluate the potential joint effect of C-peptide, IGFs and energy balance on the etiology of breast cancer. In this application we have included 528 C-peptide case controls pairs and 196 IGF1, IGF2, and IGFBP3 pairs case-control pairs to evaluate the joint effect of IGFs and C-peptide considering body weight and body fat distribution relative to energy intake and expenditure, and the combined effect of these four factors (dietary, PA, BMI, WHR using data collected from the Shanghai Breast Cancer Study. This epidemiologic study has the resources to evaluate biomarkers in both blood and urine for breast cancer. In over 50% of the cancer cases, biospecimen collections and in-person interviews were completed before any cancer treatment.

Body

Approved Statement of Work

Task 1. Undergo intensive course training in epidemiology, biostatistics, and molecular biology, Months 1-24:

1a. Take 2 courses in the Vanderbilt School of Medicine, Department of Preventive Medicine (Spring Semester, 2002), Epidemiology 2 (3 credits) and Biostatistics 2 (3 credits): Months 1-5.

1b. Take 1 course in the Vanderbilt School of Medicine, Department of Preventive Medicine (Spring Semester, 2002), Grant Writing (1 credit),

1c. Take 1 course in the Vanderbilt Department of Molecular Biology,: Cancer Biology (4 credits): Months 13-18.

Body

Approved Statement of Work

Task 1. 1d. Take 1 course in the Vanderbilt Department of Molecular Physiology and Biophysics, (Fall Semester, 2003), Molecular Endocrinology (2 credits): Months 21-24.

Task 2. Undergo extensive research training in the aspect of the association of C-peptide, IGFs, and energy balance with breast cancer risk: Months 1-36.

2a. Analyze data from The Shanghai Breast Cancer Study (1500 cases and 1500 controls to evaluate the association between energy balance and breast cancer risk and prepare a manuscript to report the findings: Months 1-8.

2b. Design a case-control study within the Shanghai Breast Cancer Study(400 cases and 400 controls) to evaluate the association of C-peptide, and IGFs with breast cancer risk and prepare blood samples for relevant assays: Months 1-6.

2c. Analyze and publish the relationship between C-peptide and breast cancer risk: Months 12-18.

2d. Analyze and publish the joint effect of C-peptide with IGFs on breast cancer risk: Months 15-20.

2e. Analyze and publish the relationship of diet, physical activity, body mass index (BMI), and waist-to-hip ratio (WHR) with C-peptide and IGFs: Months 20-36.

Task 3. Prepare grant proposal for continuation

3a. Develop and submit a grant proposal to expand the sample size of the study to evaluate C-peptide, IGF, estrogen, and phytoestrogens in relation to breast cancer risk: Months 24-30.

Key Research Accomplishments:

- **September 2001**: Completed Biostatistics 1 course in the Department of Preventive Medicine.
- **October 2001**: Presented abstract entitled "Body weight and body fat distribution in relation to lifestyle factors among Chinese women in Shanghai" at the North American Association for the Study of Obesity, Québec City, Canada.
- **January 2002**: Began designing case-control sub-study on IGF, C-peptide and breast cancer risk from the Shanghai Breast Cancer Study (parent study).
- **February 2002**: Completed Biostatistics 2 course in the Department of Preventive Medicine.
- **March 2002**: Completed Epidemiology 2 course in the Department of Preventive Medicine.
- **March 2002**: Coordinated delivery of 724 blood samples from the Vanderbilt Ingram Cancer Center laboratory to Dr. Herbert Yu (consultant) at Yale University Department of Epidemiology and Public Health, for relevant assay analysis.
- **April 2002**: Prepared manuscript entitled "Intake of fruits, vegetables, and selected micronutrients in relation to the risk of breast cancer " utilizing data from the Shanghai Breast Cancer Study for submission to the *International Journal of Cancer*. (Please see appendix 1).

- **April 2002**: Through collaboration with Dr. Herbert Yu in the Yale University Department of Epidemiology and Public Health, completed lab analysis on blood samples (528 C-peptide case controls pairs and 196 IGF1, IGF2, and IGFBP3 pairs) for relevant assays within the Shanghai Breast Cancer Study case-control study to evaluate the association of C-peptide, and IGFs with breast cancer risk.
- **April 2002**: Started analysis of joint effect of C-Peptide, IGFs and energy balance on breast cancer risk.

Reportable Outcomes:

- The additional biostatistics and epidemiology training provided through the Vanderbilt Preventive Medicine department, Masters in Public Health program has enabled me to independently perform statistical analysis on SAS and Stata as well as coordinate and implement a five hospital case-control study in Nashville, Tennessee entitled the "Nashville Breast Health Study".
- I have presented an abstract at the North American Association for the Study of Obesity (NAASO) that examined the association between body fat distribution and lifestyle factors of women residing in Shanghai, China.
- I have prepared and submitted a manuscript on the association of vegetable, fruit and vitamin intake with breast cancer risk using data from the Shanghai Breast Cancer case-control study.
- I am currently preparing a manuscript on the relationship between body distribution and obesity related comorbidities in a population of women residing in Shanghai, China.
- I have designed and implemented a sub-study within the Shanghai Breast Cancer case-control study to evaluate the joint effects of C-peptide, and IGF1, IGF2 and IGFBP3 on breast cancer risk. In addition, the sub-study will function to enhance the statistical power of the parent study. The Shanghai Breast Cancer study has completed assays of C-peptide for 143 case-control pairs and IGF1, IGF2, and IGFBP3 for 300 case-control pairs. To enhance the statistical power of this study for evaluating joint effects of these biomarkers, this proposal has facilitated additional C-peptide assays for 514 (257 pairs) samples and 300 assays for an additional 200 samples (100 pairs) to bring the total sample size to 400 case-control pairs.

Conclusions:

- The additional training in biostatistics and epidemiology has enhanced my doctoral training in Health Promotion and Education. This in turn has enabled me to independently conduct statistical analyses, establish epidemiologic case-control studies in Nashville, TN and create a sub-study within a pre-existing case-control study located in Shanghai, China.

- Results from my manuscript on fruit, vegetable and micronutrient intake in women in Shanghai, China reveal a significant inverse relationship between breast cancer risk and intake of certain dark green vegetables, dark yellow-orange vegetables, and Chinese white turnips, and all individual fruits except for watermelon and apples. Of the micronutrients examined, dietary vitamin E was related to a reduced risk of breast cancer.

Appendix 1
Manuscript submitted to International Journal of Cancer

Intake of fruits, vegetables, and selected micronutrients in relation to the risk of breast cancer

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Keywords: Fruit, vegetable, micronutrient intake and breast cancer risk

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ABSTRACT

High fruit and vegetable intake has been linked with a reduced risk of breast cancer, but evidence was not entirely consistent. We investigated the associations of breast cancer risk with vegetables, fruits and related micronutrient intake in a population-based case-control study among Chinese women in Shanghai, where dietary patterns differ substantially from other study populations. Included in the study were 1,459 incident breast cancer cases and 1,556 frequency–matched controls. Usual dietary habits were assessed by in-person interviews. Logistic regression was used to compute adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to measure strength of the associations. There was no association between breast cancer risk and total vegetable intake. However, the risk of breast cancer declined with increasing intake of dark yellow-orange vegetables (trend test, $p=0.02$) and Chinese white turnips (trend test, $p\leq0.001$) with adjusted ORs in the highest quintile being 0.79 (95% CI =0.60-0.98) and 0.67(95% CI =0.53-0.85), respectively. Intake of fruits, except watermelons and apples, was inversely associated with breast cancer risk (p values for trend tests, ≤0.05). This study suggests that high intake of certain vegetables and fruits may be associated with a reduced risk of breast cancer.

INTRODUCTION

Vegetables and fruits contain numerous bioactive and potentially anticarcinogenic substances including carotenes, dithiolthiones, flavoids, indoles, isothiocyanates, phenols, folic acid, and vitamins C and E.[1] There are many possible mechanisms by which the above substances might inhibit carcinogenesis, such as, antioxidant effects, increases in cell-to-cell communication, activation of enzymes involved in carcinogen detoxification, alteration of estrogen metabolism, effects on DNA methlylation and repair, and antiproliferative effects.[2] Epidemiologic studies on the relationships of intake of vegetables and fruit with breast cancer risk, however, have not been consistent. Approximately 35 studies have evaluated the association between intake of fruits and vegetables and breast cancer risk. Fifteen studies reported an inverse association with vegetables intake and nine studies found a decreased risk with high fruit intake.[3-17,23] The results from previous studies on micronutrients such as vitamin A, C, and E and carotene have also been inconsistent.[3-6,12,15-22,24-25] A recent pooled analysis of eight cohort studies showed no significant association between fruit and vegetable intake and breast cancer risk.[26] Virtually all previous studies, however, were conducted among Caucasian women; and many studies evaluated only a limited number of food items. We report here results from a large population-based case-control study conducted among Chinese women in Shanghai, where the incidence rate of breast cancer is about one-third the rate in US white women and certain fruits and vegetables are highly consumed. Inherent in the Shanghai population are dietary practices and foods, which are not represented by previous studies conducted in western society.

MATERIALS AND METHODS

The Shanghai Breast Cancer Study, a population-based case-control study, was designed to recruit women aged 25-64 who were newly diagnosed with breast cancer between August 1996 and

March 1998. All study subjects were permanent residents of urban Shanghai. They had no prior history of cancer and were alive at the time of interview. Through a rapid case-ascertainment system, supplemented by the population-based Shanghai Cancer Registry, 1,602 eligible breast cancer cases were identified during the study period and in-person interviews were completed for 1,459 (91.1%) of the eligible cases. The major reasons for non-participation were refusal (109 cases, 6.8%), death prior to interview (17 cases, 1.1%), and inability to locate (17 cases, 1.1%). Two senior pathologists confirmed all diagnoses through review of slides.

The Shanghai Resident Registry, which registers all permanent residents in urban Shanghai, was used to randomly select controls from female residents, frequency-matched to cases by age (5-year intervals). The number of controls in each age-specific stratum was determined in advance according to the age distribution of the incident breast cancer cases reported to the Shanghai Cancer Registry from 1990-1993. Only women who lived at the address held by the registry during the study period were considered eligible for the study. In-person interviews were completed with 1,556 (90.3%) of the 1,724 eligible controls identified. Reasons for non-participation included refusal (166 controls, 9.6%) or death (2 controls, 0.1%).

Trained interviewers measured weight, circumference of waist and hips, sitting and standing heights and conducted a in-person interview according to a standard protocol. A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight, and family history of cancer. Information on usual adult dietary intake was collected using a comprehensive quantitative food frequency questionnaire (FFQ). This FFQ was developed based on data from a 24-hour dietary recall surveys and includes 76 food items that cover over 85% of foods consumed in Shanghai.[17]

Of these 76 food items, 30 are fresh vegetable food items and 8 are fruit items. During the interview, each study participant was first asked how frequently she consumed a specific food or a group of foods, (e.g. daily, weekly, monthly, yearly, or never) followed by a question on how many liangs (= 50 grams) of food eaten per unit of time (day, week, month, or year) in the previous five-year period, ignoring any recent changes.

Total intake of vitamin A (mg), including carotene and retinol, vitamin C (mg) and vitamin E (mg) was calculated based on data from the Chinese Food Composition Table. [17] Statistical analyses were conducted using SAS Version 8.0 (SAS Institute, Cary, NC). Quintile distributions among controls were used to categorize the dietary-intake variables. Odds ratios were used to measure the association of breast cancer risk with intake of selected food groups and vitamins. Unconditional logistic regression was used to model the association between intake of selected vegetables and fruits, micronutrients and breast cancer risk. Maximum likelihood estimates of the odds ratios and 95 % confidence intervals (CIs) were calculated adjusting for potential confounding variables. Age was included as a continuous variable throughout data analyses. Trend tests were conducted by treating categorical variables as the ordinal values of the quintile levels in the models. Analyses were also stratified by menopausal status. All statistical tests were based on two-sided probability.

RESULTS

Table 1 shows comparisons of cases and controls on selected demographic factors, known risk factors of breast cancer, total energy and fat intake. Compared to controls, cases had earlier age at menarche, later age at menopause and later age at first live birth. Cases were more likely to have a higher education, a family history of breast cancer among first-degree relatives, a history of breast fibroadenoma, a higher body mass index (BMI), a higher waist-hip-ratio (WHR), and were less likely to exercise in the past 10 years. All of the above variables were considered potential confounders and

adjusted for in subsequent analyses. No significant differences between cases and controls were observed for family income, adult height, usual intake of energy and fat, or percentage of calories as fat.

Among controls, the median intake of total vegetables consumed was 270 grams per day, with the major contributing food item being dark green vegetables (33%) including bok choy (28%)(Table 2). Total mean fruit intake was 223 grams per day with watermelon comprising 54% of fruit intake by weight.

Overall, there was no association between total vegetable intake and breast cancer risk (Table 3). Increased consumption of dark green vegetables (other than bok choy), dark yellow-orange vegetables and white turnips, however, was inversely associated with breast cancer risk. The odds ratio and 95% confidence intervals for the highest quintile intake of these vegetables were 0.65 ($p \leq 0.001$), 0.79 ($p=0.02$) and 0.67 ($p \leq 0.001$), respectively. Total fruit consumption was not associated with breast cancer risk. Intakes of all individual fruits, except watermelon and apple, had an inverse association with breast cancer risk. Total fruits without watermelon displayed a strong significant inverse association (OR=0.77, 95% CI=0.60-0.98) (trend test $p=0.02$).

Further analyses were conducted stratified by menopausal status (data not shown on tables). With the exception of dark yellow-orange vegetables and citrus fruits, findings were consistent among pre- and postmenopausal women. Both dark yellow-orange vegetables and citrus fruits were found to be inversely associated with breast cancer risk among pre-menopausal women, with adjusted ORs in the highest quintile being 0.66 (95% CI=0.49-0.96) for dark yellow-orange vegetables (trend test, $p=0.003$) and 0.65 (95% CI=0.48-0.88) for citrus fruits (trend test, $p=<0.001$). These inverse associations, however, were not statistically significant in post-menopausal women.

Odds ratios associated with intake of selected micronutrients are shown in Table 4. A significant inverse association between vitamin E intake and breast cancer risk was found (trend test p=0.03). There was little evidence of any association of breast cancer risk with intake of carotene, vitamin C, and total vitamin A.

DISCUSSION

This large population-based case-control study was conducted among Chinese women in Shanghai, a population with an abundant fruit and vegetable intake but of low vitamin supplement usage. The results of this study suggest no overall association of breast cancer risk with total fruit or vegetable intake. However, a significant inverse relationship was observed between breast cancer risk and intake of certain dark green vegetables, dark yellow-orange vegetables, and Chinese white turnips, and all individual fruits except for watermelon and apples. Of the micronutrients examined, dietary vitamin E was related to a reduced risk of breast cancer.

High intake of fruits and vegetables have been consistently shown to be associated with a reduced risk of several cancers, including cancers of the lung, oral cavity, pancreas, larynx, esophagus, bladder, and stomach.[1,28-29] However, results from previous epidemiological studies on vegetables and fruits with breast cancer have been inconsistent. At least nine case-control studies have reported an inverse association of breast cancer with higher intake of fruits and vegetables.[3,6,11-13,31] Other studies[5,24,38]reported a non-significant inverse association. A recent pooled analysis of cohort studies found that neither fruit nor vegetable intake was associated with breast cancer risk.[26] These cohort studies, however, were conducted in western society where the intake level of fruits and vegetables is relatively homogenous and consumption indigenous Chinese vegetables such as white turnip are low. Further, the quality of dietary data from these cohort studies also differ, as some studies included fewer

than 12 food items in the dietary assessment. Vitamin supplements are widely used in many western societies, and some foods are fortified with various vitamins, such as folic acids. These all affect observational epidemiologic studies to evaluate dietary factors in relation to cancer risk. Most Chinese women have diets composed mainly of unprocessed and unfortified foods, and few Chinese women take vitamin supplements; this allows better assessment of nutrient intake and minimizes potential misclassification.[2]

Consumption of both dark green (other than bok choy) and yellow-orange vegetables in our study were inversely related with breast cancer risk. These findings are consistent with several other epidemiologic studies investigating the relationship between dietary intake of dark green vegetables and risk of breast cancer. [7,9,11,14] Dark green/ yellow-orange vegetables contain high levels of α- and β-carotenes. These carotenoids may protect against cancer via their ability to block damage by free radicals. β –carotene can be metabolized into vitamin A which plays a role in differentiation of normal epithelial cells. In addition to β –carotene, dark green-leafy vegetables also have a high level of folate and lutein, the latter being an antioxidant carotenoid that has been shown to have cancer inhibitory effects *in vitro* and animal experiments.[1] High intake of folate has been shown to be inversely associated with breast cancer risk in several epidemiologic studies, including the case-control study we conducted in Shanghai.[2,15,17,23]

Although bok choy accounts for over 25% of the overall vegetable intake for Chinese dark green vegetables, it was not associated with breast cancer risk. There is no immediate explanation for this finding. Potential misclassification error for assessing intake level of this vegetable may be high, as this food is consumed in large quantities and high frequency.[2]

In contrast to findings from several other studies[16,20,33-34] we did not find an inverse association of intakes of cruciferous vegetables or legumes with breast cancer risk. Chinese white turnip intake,

however, was inversely associated with breast cancer risk. Similar findings were reported from previous studies on oral and pharyngeal cancers.[35-36] Although there is no existing research on the association between breast cancer and white turnips, some phytochemicals in white turnips may be protective. Of them, kaempferol, a flavonoid, has been shown to have cancer inhibitory effects.[37-38]

With the exception of watermelon and apple, inverse associations of breast cancer risk were found for intakes of virtually all fruits evaluated in our study , with the strongest association being citrus fruits. Citrus fruits are known for their high content of vitamin C which may protect cell membranes and DNA from oxidative damage.[39] More recently, a wide variety of flavonoids have been identified in citrus fruits, which may also act as antioxidants.[14-15] Other fruits have also been shown to be associated with a reduced risk of breast cancer in previous studies, although evidence has not been entirely consistent. Watermelon, consumed in large quantity in Shanghai, was not found to be related to breast cancer risk in the study. The reason for a lack of association with this fruit is unknown, but measurement error in assessing intake level of watermelon may have contributed to the null association, since foods that are consumed in such a high quantity may be difficult to assess with accuracy.

Our study suggested that breast cancer risk may be inversely related to the intake of vitamin E. Vitamin E is a fat soluable vitamin best characterized as a lipid-soluble antioxidant that protects against lipid peroxidation of cell membranes. It also inhibits formulation of carcinogenic nitrosoamines and nitrosoamides.[40] Previous observational studies have shown either inverse or no association of vitamin E with breast cancer risk. [15-18,21-23,41-43,45] Freudenheim and colleagues (1996) found a reduction in risk of breast cancer associated with food sources of vitamin E but not with supplements. A case-control study conducted in Uruguay by Ronco et al., (1999) showed a significant inverse association with breast cancer risk and vitamin E. Odds ratios for the highest vs. lowest quartile were 0.40

(95%CI=0.30-0.60) (trend test, $p \leq 0.001$). No significant associations were observed for dietary intake of vitamin E and breast cancer risk in several prospective studies, including the Netherlands Cohort study[43] the Nurses' Health Study,[5] the Iowa Women's Health Study,[41] and the New York State Cohort Study.[44]

The primary concerns of this study are potential selection and recall bias. Since this is a population-based case-control study with high response rates (91.1% and 90.3%, for cases and controls respectively), the threat of selection bias is limited. As in virtually all case-control studies, this study relies on self-reporting of past dietary habits. Patients with cancer may recall diet in a different way than controls, because of the cancer diagnosis and treatments.[23] However, approximately 80% of the cases from Shanghai were interviewed within four months of their cancer diagnosis, which limited potential errors in recall of usual diets prior to disease diagnosis. Misclassification error in dietary assessment is another concern similar to all observational studies of dietary factors. Non-differential misclassification usually attenuates the true association, suggesting that some of the null associations observed in this study may be due to errors in dietary assessment.

Because all intakes were calculated from a food-frequency questionnaire, caution should be exercised in the interpretation of the quantities presented. While food-frequency questionnaires have been shown to be valid and reliable in ranking individuals in terms of consumption, they are less valid for the quantification of intake. Furthermore, observational studies cannot disentangle whether some known food constituents (e.g. vitamins) themselves are protective or whether they are serving as markers of unidentified components in vegetable and fruit.

In summary, this population-based case-control study revealed that dietary intake of certain vegetables and fruits and vitamin E were inversely associated with the risk of breast cancer. Some of

these food groups contain high levels of non-nutritive substances such as flavonoids, sulfa compounds and indoles, suggesting that these phytochemicals may be protective against breast cancer.

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TABLE 1. Comparison of cases and controls on demographics and selected breast cancer risk factors, The Shanghai Breast Cancer Study, 1996-1998.

	Cases† (n=1459)	Controls† (n=1556)	P-value
Age	47.8±8.0	47.2±8.8	0.03
Education (%)			
No formal education	3.6	5.5	0.01
Elementary school	8.5	8.4	
Middle + high school	74.3	75.4	
Profession, college and above	13.6	10.7	
Per capita income (Yuan) (%)			0.05
<4000	19.8	18.2	
4000-5999	31.7	31.9	
6000-7999	13.0	13.9	
8000-8999	20.2	23.5	
≥9000	15.2	12.4	
Breast cancer in first degree relatives (%)	3.7	2.4	0.05
Ever had breast fibroadenoma (%)	9.6	5.0	<0.01
Exercised regularly (%)	18.8	25.2	<0.01
Body mass index	23.5±3.4	23.1±3.4	<0.01
Waist-to-hip ratio	0.81±0.06	0.80±0.06	<0.01
Nulliparous (%)	5.1	3.9	0.13
Age at first live birth‡ (years)	26.8±4.2	26.2±3.9	<0.01
Menarcheal age (years)	14.5±1.6	14.7±1.7	<0.01
Menopausal age§ (years)	48.1±4.6	47.5±4.9	0.02
Energy intake (kcal/day)	1871±464.5	1845.1.±463.6	0.13
Total fat intake (g/day)	36.3±17.4	35.3±16.2	0.08
Total percentage of fat calories (kcal/day)	17.1%	16.9%	0.43

Subjects with missing values were excluded from the analysis

†Unless otherwise specified, mean ±SD are presented.

‡Among women who had live births.

§ Among post-menopausal women.

TABLE 2. Intake of fruit/vegetable among controls in The Shanghai Breast Cancer Study, 1996-1998.

Items	Vegetables(g/day) Mean ± SD	%	Items	Fruits (g/day) Mean± SD	%
Total Vegetables	269.6±167.1		**Total Fruits**	223.3±170.5	
Dark Green[†]	88.4 1±70.3	33%	Citrus Fruits[§§]	20.2±25.7	9%
Bok Choy	75.0± 62.0	28%	Apples	32.0±39.8	14%
Others	13.4±30.7	5%	Watermelon	119.2±103.4	53%
Dark Yellow[‡]	6.6±14.7	2%	Grapes	8.9±20.0	4%
Cruciferous§	98.8 ± 71.7	37%	Bananas	8.9±17.6	4%
Fresh Legumes[¶]	21.2 ± 29.5	8%	Peach	6.8±13.8	3%
Allium[#]	8.8 ± 9.5	3%	Pear	16.8±23.8	8%
Mushrooms	7.6 ± 12.8	3%	Others[¶¶]	10.3±19.3	5%
White Turnip	4.3 ± 9.0	2%			
Tomatoes	30.8 ±43.7	11%			
Melons[††]	43.3±46.2	16%			
Others[‡‡]	37.7±33.3	14%			

[†]Dark Green vegetables: bok choy, spinach, fresh green pepper, garlic shoots, chives, scallions, Chinese celery
[‡]Dark Yellow: carrots, sweet potato
[§]Cruciferous vegetables: bok choy, cabbage, napa cabbage, cauliflower, Chinese white turnip
¶Fresh Legumes: fresh soybean, fresh broad beans, yard long bean, green bean, hyacinth bean/snow peas,
#Allium vegetables: garlic, head of garlic, chives, scallions, garlic shoots
[††]Melons: Winter melon, cucumber, wax gourd
[‡‡]Other Vegetables: potato, eggplant, corn, ginger, lotus root, wild rice stems, asparagus lettuce, bamboo shoots
[§§]Citrus Fruits: tangerines, oranges, grapefruits
¶¶Other Fruits: strawberries, cantaloupe
Vegetable items are grouped in more than one category and add up to more than 100%

TABLE 3. Adjusted Odds Ratios (ORs) and 95% CIs for the association of breast cancer risk with the intake level of selected fruits and vegetable groups, Shanghai Breast Cancer Study, 1996-1998.

	Q1(low)	Q2	Q3	Q4	Q5	P-value trend test
Total Vegetable	1.00	0.98(0.78-1.25)	1.11(0.88-1.40)	0.97(0.76-1.23)	1.05(0.81-1.40)	0.81
Dark green	1.00	1.04(0.83-1.30)	0.89(0.71-1.12)	0.97(0.78-1.22)	1.02(0.82-1.28)	0.83
Bok Choy	1.00	1.25(1.00-1.57)	1.07(0.86-1.34)	1.22(0.97-1.53)	1.23(0.95-1.60)	0.16
Other	1.00	0.83(0.66-1.04)	0.75(0.60-0.94)	0.69(0.54-0.87)	0.65(0.51-0.83)	<0.001
Dark Yellow	1.00	0.89(0.70-1.11)	0.90(0.71-1.13)	0.77(0.61-0.97)	0.79(0.60-0.98)	0.02
Cruciferous	1.00	1.05(0.82-1.30)	1.03(0.81-1.30)	1.20(0.95-1.52)	1.10(0.87-1.40)	0.21
Legumes	1.00	1.01(0.80-1.27)	0.87(0.68-1.10)	0.95(0.75-1.19)	0.89(0.70-1.14)	0.29
Allium	1.00	0.94(0.75-1.18)	0.83(0.66-1.03)	0.75(0.60-0.94)	0.91(0.73-1.14)	0.10
Others						
Mushrooms	1.00	1.07(0.85-1.34)	0.89(0.70-1.12)	0.92(0.73-1.16)	0.96(0.76-1.22)	0.41
White Turnip	1.00	0.69(0.56-0.86)	0.66(0.52-0.83)	0.58(0.46-0.74)	0.67(0.53-0.85)	<0.001
Tomato	1.00	1.06(0.84-1.33)	0.92(0.73-1.16)	1.02(0.80-1.29)	1.19(0.94-1.51)	0.24
Melons	1.00	0.88(0.69-1.12)	1.11(0.88-1.40)	1.12(0.88-1.41)	1.12(0.89-1.43)	0.09
Total Fruits	1.00	0.86(0.68-1.08)	0.83(0.66-1.05)	0.87(0.69-1.11)	1.01(0.80-1.28)	0.89
Citrus Fruits	1.00	0.83(0.66-1.04)	0.75(0.60-0.94)	0.67(0.53-0.85)	0.68(0.54-0.86)	0.002
Apples	1.00	1.11(0.89-1.38)	0.96(0.75-1.22)	0.93(0.74-1.17)	0.86(0.66-1.11)	0.09
Grapes	1.00	1.03(0.82-1.30)	0.88(0.70-1.10)	0.81(0.64-1.03)	0.86(0.68-1.10)	0.05
Banana	1.00	0.89(0.71-1.12)	0.77(0.62-0.96)	0.62(0.49-0.80)	0.73(0.58-0.93)	<0.001
Watermelon	1.00	0.83(0.66-1.04)	0.93(0.76-1.14)	0.94(0.67-1.31)	1.17(0.94-1.47)	0.08
Peach	1.00	0.89(0.70-1.12)	0.76(0.61-0.95)	0.67(0.53-0.84)	0.83(0.67-1.04)	<0.001
Pear	1.00	0.99(0.79-1.25)	1.06(0.85-1.33)	0.79(0.63-0.99)	0.86(0.67-1.09)	0.05
Other	1.00	0.88(0.70-1.11)	0.89(0.71-1.11)	0.80(0.63-1.02)	0.76(0.60-0.97)	0.02
Total Fruits without watermelon	1.00	0.92(0.73-1.15)	0.78(0.62-0.99)	0.80(0.64-1.01)	0.77(0.60-0.98)	0.02

*Odds ratios were adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, waist-to-hip ratio, menarche age, physical activity, ever had live birth, age at first live birth, menopausal status, menopausal age, and total energy compared to the lowest quintile group.

TABLE 4. Dietary intake of selected carotenes and the risk of breast cancer, The Shanghai Breast Cancer Study, 1996-1998.0

	Adjusted ORs (95% confidence interval) by quintile Total Dietary Intake					
	Q1 (Low)	Q2	Q3	Q4	Q5	P-value trend test
			All	Subjects		
Vitamin A	1.00	0.96(0.76-1.22)	0.90(0.71-1.14)	0.90(0.70-1.15)	0.97(0.75-1.25)	0.66
Retinol	1.00	1.24(0.98-1.56)	1.08(0.85-1.37)	1.13(0.88-1.44)	1.12(0.87-1.45)	0.67
Carotene	1.00	1.04(0.82-1.31)	1.22(0.97-1.53)	0.89(0.69-1.13)	1.17(0.92-1.48)	0.55
Vitamin C	1.00	0.84(0.67-1.07)	0.93(0.73-1.17)	0.96(0.76-1.21)	0.92(0.72-1.18)	0.88
Vitamin E	1.00	0.99(0.78-1.25)	1.18(0.93-1.50)	0.81(0.63-1.05)	0.73(0.54-0.98)	0.03
			Premenopausal	Women		
Vitamin A	1.00	0.93(0.68- 1.25)	0.90(0.66-1.22)	0.76 (0.561.04)	0.81(0.59-1.11)	0.09
Retinol	1.00	1.01(0.81-1.46)	0.94(0.69-1.27)	1.02(0.75-1.38)	0.95(0.69-1.31)	0.64
Carotene	1.00	1.10(0.82-1.46)	1.10(0.81-1.44)	0.87(0.64-1.20)	1.15(0.85-1.56)	0.88
Vitamin C	1.00	0.84(0.63-1.13)	0.82(0.61-1.10)	0.96(0.71-1.29)	0.92(0.67-1.26)	0.93
Vitamin E	1.00	0.87(0.65-1.17)	1.02(0.76-1.40)	0.76(0.55-1.05)	0.75(0.51-1.10)	0.12
			Postmenopausal	Women		
Vitamin A	1.00	1.05(0.72-1.53)	0.90(0.61-1.33)	1.22(0.81-1.84)	1.48(0.94-2.33)	0.10
Retinol	1.00	1.65(1.14 -2.40)	1.48 (1.02- 2.16	1.29 (0.891.89)	1.45(0.98-2.13)	0.23
Carotene	1.00	0.92(0.62-1.37)	1.54(1.03-2.29)	0.90(0.60-1.34)	1.24(0.83-1.84)	0.38
Vitamin C	1.00	0.85(0.57-1.25)	1.14(0.76-1.69)	0.92(0.63-1.37)	0.97(0.65-1.46)	0.99
Vitamin E	1.00	1.26(0.84-1.90)	1.59(1.06-2.38)	0.95(0.62-1.47)	0.77(0.48-1.25)	0.20

*Odds ratios were compared to the lowest quintile and adjusted for age, education, family history of breast cancer, history of breast fibroadenoma waist-to-hip ratio, menarche age, physical activity, ever had live birth, age at first live birth, menopausal status, menopausal age, and total energy